REMARKS

As correctly stated in the Official Action, claims 1-3 and 7-9 are pending in the application. Claims 4-6 have been withdrawn from consideration. Claims 1-3 and 7-9 stand rejected. Applicants respectfully request reconsideration of the rejections of the claims in view of the following comments.

Rejections Under 35 U.S.C. § 103(a)

Claims 1-3 and 7-9 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Harris *et al.* (U.S. 6,200,955) in view of Eran *et al.* (H1509) and in further view of Aston (US 5,506,204). This rejection is respectfully traversed.

Applicants respectfully submit that the combination of Harris, Eran, and Aston does not meet the standard for a *prima facie* case of obviousness. (1) There is no suggestion or motivation, either in the cited publications themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the publications or to combine their teachings, to arrive at the method of claims 1-3 and 7-9, (2) there is no reasonable expectation of success in practicing the method of claim 1-3 and 7-9, and (3) the cited publication (or publications when combined) do not teach or suggest all the limitations of claims 7-9.

In particular, Applicants respectfully submit that there is no suggestion or motivation to modify Harris, or to combine its teachings with that of Eran and/or Aston, to arrive at the method of claim 1-3 or 7-9, considering the state of the art. The Examiner concedes, at pp. 4-5 of the Official Action, that neither Harris *et al.* '153 nor Harris *et al.* '955 teach a method of administering the peptides claimed

therein to treat sepsis. At pp. 4-5 of the Official action, the Examiner relies on Eran *et al.* for the proposition that "it is known in the art that heparin binds to fibronectin and leads to reduced levels of fibronectin which have been found in patients with sepsis and that the replenishment of fibronectin, by blocking the action of heparin via a heparin antagonist, for example, treats sepsis and leads to clinical improvement."

However, the mechanism of action of the peptides recited in the claimed methods involves the direct binding of the peptides to endotoxin, as described in the specification, for example at page 4, lines 5-28, and Examples 1-3. In contrast, the cited Harris, Eran and Aston publications do not relate to the binding of the peptides to endotoxin, but rather involve the use of peptides as heparin antagonists and the effects of altering heparin binding to fibronectin. In the experiments as described in Examples 1-3 of the specification, peptide binding to endotoxin was measured either in the presence of plasma, or in a buffered solution. The binding of the peptides to endotoxin was not dependent on the presence of heparin. Furthermore, the binding of the peptide to endotoxin was not dependent on altering heparin binding to fibronectin. Thus, the claimed methods do not involve the use of the peptide as a heparin antagonist or altering the binding of heparin to fibronectin, as discussed by Harris, Eran and Aston.

Moreover, the documents attached hereto indicate that treatment of septic shock with replenishment of fibronectin was not considered to be a convincing treatment by those of ordinary skill in the art (see Putterman, 1990, Am J. Emerg Med., 8:152-161, and Powell *et al.*, 1991, Vox Sang., 60:193-202). Considering the state of the art as shown by Putterman and by Powell, there is no suggestion or motivation, either in the cited publications themselves or in th knowledge generally available to one of ordinary skill in the art, to modify th teachings of those

publications or to combine publication teachings, to suggest the method of claims 1-3, or 7-9.

Moreover, Applicants respectfully submit that there is no reasonable expectation that the combination of the publications would successfully achieve the method of claims 1-3, or 7-9. At page 5 of the Official Action, it is argued that "[i]t is known in the art that heparin binds to fibronectin and leads to reduced levels of fibronectin which have been found in patients with sepsis and that the replenishment of fibronectin, by blocking the action of heparin via a heparin antagonist, for example, treats sepsis and leads to clinical improvement of such patients." However, Putterman and Powell indicate that the art of the time was not convincing that replenishment of fibronectin treats sepsis and leads to clinical improvement of such patients. Accordingly, there is no reasonable expectation that the combination of the teachings of the cited publications would successfully achieve the method of claims 1-3, or 7-9.

In addition, Applicants respectfully submit that Harris, Eran, and Aston do not teach or suggest all the limitations of claims 7-9. Neither Harris, Eran, nor Aston is related to methods for reducing endotoxin levels in the body of a patient, as required by Claim 7. The cited publications thus do not teach all the claim limitations of claims 7-9.

As (1) there is no suggestion, either in the cited publications themselves or in the art generally to modify or combine the teachings of Harris, Eran, and Aston to arrive at the method of claims 1-3, or 7-9, considering the state of the art; (2) there is no reasonable expectation that the combination of Harris, Eran, and Aston would successfully achieve the method of claims 1-3, or 7-9; and (3) Harris, Eran, and Aston do not teach or suggest all the limitations of claims 7-9, a *prima facie* case of

obviousness under 35 U.S.C. § 103(a) has not been established. Accordingly, withdrawal of this rejection is respectfully requested.

Obviousness-type Double Patenting Rejections

Claims 1-3 and 7-9 stand rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-3 of U.S. Patent No. 5,877,153 (Harris *et al.*) in view of Eran *et al.* (H1509) and in further view of Aston (US 5,506,204). Claims 1-3 and 7-9 also stand rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-4 of U.S. Patent No. 6,200,955 (Harris *et al.*) in view of Eran *et al.* (H1509) and in further view of Aston (US 5,506,204). These rejections are also traversed, for the reasons set forth in detail above. For those reasons, applicants respectfully submit that Harris (5,877,153) or Harris (6,200,955), Eran, and Aston do not meet the standard for a *prima facie* case of obviousness. Accordingly, withdrawal of this rejection is respectfully requested.

CONCLUSIONS

From the foregoing, further and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

In the event that there are any questions concerning this response or the application in general, the Examiner is respectfully requested to telephone the undersigned so that prosecution of the application may be expedited.

Respectfully submitted,

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I hereby certify that this correspondence is being filed by facsimile transmission to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA. 22313-1450, to facsimile number 1.703.872.9306 on this date, November 14, 2003.
by Sandra B. Paye
Sandra B. Paye

Entrez-PubMed

1: Am J Emerg Med. 1990 Mar;8(2):152-61. Related Articles, Lin

Modern approaches to the therapy of septic shock.

Putterman C.

Department of Internal Medicine A, Haddassah University Hospital--Ein Kerum, Jerusalem, Israel.

Bacteremia from gram-negative rods is a great cause of concern for hospital physicians today. Shock-complicating gram-negative sepsis has a mortality rate of 60% and above, despite early diagnosis and treatment. Intensive research efforts have shown new pathophysiological mechanisms and mediators involved in septic shock, with changes in recommended treatment protocols. In this report, the authors review the use of corticosteroids, fibronectin, naloxone hydrochloride, and immunotherapy, with emphasis on theoretical considerations and relevant clinical experience. Although these treatment methods may have been promising initially, data from large double blind human trials are either lacking or unencouraging. While continued research and modern therapeutic approaches should improve future survival rates from septic shock, use of the therapies reviewed should be considered experimental at this time.

Publication Types:
- Review
- Review, Tutorial

PMID: 2405867 [PubMed - indexed for MEDLINE]

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Entrez-PubMed

1: Vox Sang. 1991;60(4):193-202.

Current status of fibronectin in transfusion medicine: focus on clinical studies.

Powell FS, Doran JE.

Department of Experimental Medicine, Swiss Red Cross Transfusion Service Berne.

It has long been hypothesized that fibronectin (Fn) is essential to the function of the reticuloendothelial system (RES) and that the reversal of Fn deficiency in critically ill patients would result in a clinical benefit to these patients. Fn administration to deficient patients was postulated to improve the function of the RES, decrease the incidence of organ failure, sepsis and ultimately mortality. Over the past 15 years, several clinical studies have been performe to test these hypotheses. The initial anecdotal studies using cryoprecipitate (a plasma fraction enriched in Fn) revealed promising results but were neither controlled nor blinded. Further controlled studies were published utilizing both cryoprecipitate and purified Fn. Unfortunately, the great majority of authors found no beneficial effects of Fn administration in critically ill patients, in relation to incidence of organ failure, sepsis, or mortality. These results do not support the use of Fn in this setting. Fn utilization in wound healing has shown promising results in case reports. Although its role in wound healing is not yet fully delineated, initial reports with corneal wounds show a beneficial influence of Fn administration. Further studies are needed to determine the exact function(s) of Fn in a healing wound. Efficacy must still be shown in controlled clinical trials; dosing and administration regimens need to be elucidated.

Publication Types:
- Review
- Review, Tutorial

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